Guidance for Industry

Available Therapy

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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U.S. Department of Health and Human Services
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GUIDANCE FOR INDUSTRY[1]

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This document is intended to provide guidance to industry on the meaning of the term *available therapy*, as used by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) in the Food and Drug Administration (FDA).

II. BACKGROUND

Available therapy and related terms, such as *existing treatments* and *existing therapy*, appear in a number of regulations and policy statements issued by CDER and CBER, but these terms have never been formally defined by the Agency. Some confusion has arisen regarding whether available therapy refers only to products approved by FDA for the use in question, or whether it could also refer to products used off-label or to treatments not regulated by FDA, such as surgery. This guidance document is intended to inform the public of the Agency's interpretation of *available therapy*.

III. AFFECTED REGULATIONS AND POLICY STATEMENTS

The regulations and policies described below incorporate the concept that the Agency can regulate a particular product in a certain manner because of a lack of available therapy or because of the product's advantage over available therapy. The bold italicized print highlights the importance of the availability of other products or therapies.

[1]This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

A. Treatment INDs

FDA's regulations allow the use of an investigational drug for treatment under a treatment protocol or treatment investigational new drug application (IND). The investigational drug can only be used for this purpose if the following factors are met:

- The drug is intended to treat a serious or immediately life-threatening disease.
- "***There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population***."

- The drug is being investigated under an IND in effect for the trial, or all clinical trials have been completed.

- The sponsor of the clinical trial is actively pursuing marketing approval of the investigational drug (21 CFR 312.34).

B. Subpart E Regulations

The Agency's procedures, which expedite the development, evaluation, and marketing of promising therapies to treat individuals with life-threatening and severely debilitating illnesses, reflect that the Agency must make a medical risk-benefit judgment in deciding whether to approve a drug or biological product. Under FDA regulations, as part of this risk-benefit analysis, the Agency will "tak[e] into consideration the severity of the disease and the ***absence of satisfactory alternative therapy***" (21 CFR 312.84).

C. Accelerated Approval Regulations

FDA's accelerated approval procedures are available for new drug and biological products (1) that have been studied to treat serious or life-threatening, illnesses, and (2) "that provide meaningful therapeutic benefit to patients ***over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)***" (21 CFR 314.500 and 601.40).

D. The Pediatric Rule

FDA can require the manufacturer of a marketed drug or biological product that "provides a ***meaningful therapeutic benefit over existing treatments*** for pediatric patients," but whose label does not provide adequate information to support the drug's safe and effective use in pediatric patients, to submit a

supplemental application containing data supporting the safe and effective use of the product in the pediatric population (21 CFR 201.23). Under this regulation, "a drug [product] will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that (1) if approved, ***the drug [product] would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population***...; or (2) ***the drug [product] is in a class of drugs [products] or for an indication for which there is a need for additional therapeutic options***" (21 CFR 314.55(c)(5) and 601.27(c)(5)).

E. Fast Track Drug Development Programs

FDA's fast track drug development programs are designed to facilitate the development and expedite the review of drug and biological products that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs (FDA guidance for industry on *Fast Track Drug Development Programs: Designation, Development, and Application Review* (September 1998)). In the guidance, the Agency defined an unmet medical need as a "medical need that is ***not addressed adequately by an existing therapy***."

As described in the guidance, ***where there is no available therapy for a condition, a product in a drug development plan designed to evaluate the drug's potential to address the condition would meet the factors to address an unmet medical need. Where there is available therapy for the condition, the drug development program would address unmet medical needs if it evaluated any of the following:***

- ***Improved effects on serious outcomes of the condition that are affected by alternate therapies***

- ***Effects on serious outcomes of the condition not known to be affected by the alternatives***

- ***Ability to provide benefits in patients who are unable to tolerate or are unresponsive to alternative agents, or ability to be used effectively in combination with other critical agents that cannot be combined with available therapy***

- ***Ability to provide benefits similar to those of alternatives, while avoiding serious toxicity that is present in existing***

therapies, or avoiding less serious toxicity that is common and causes discontinuation of treatment of a serious disease

- ***Ability to provide benefits similar to those of alternatives but with improvement in some factor, such as compliance or convenience, that is shown to lead to improved effects on serious outcomes*** (pp. 6-7)

F. Priority Review Policies

CDER and CBER have established review classifications of new drug applications (NDAs), Biologics License Applications (BLAs), and efficacy supplements to prioritize their review. A priority designation is intended to direct overall attention and resources to the evaluation of applications for products that have the potential for providing significant preventive or diagnostic therapeutic advance, as compared to standard applications (CDER Manual of Policies and Procedures 6020.3, Priority Review Policy, p. 2).

Products regulated by CDER are eligible for priority review if they provide a ***significant improvement compared to marketed products in the treatment, diagnosis, or prevention*** of a disease (CDER Manual of Policies and Procedures 6020.3, Priority Review Policy, p. 1). Products regulated by CBER are eligible for priority review if they provide a ***significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention*** of a serious or life-threatening disease (CBER Manual of Standard Operating Procedures and Policies 8405, Complete Review and Issuance of Action Letters, p. 2).

Most of these Agency programs are intended to encourage the development and expedite the review of innovative drug products (i.e., subpart E regulations, accelerated approval regulations, fast track drug development programs, priority review policies), while one (treatment INDs) provides early access to investigational therapies and one (the pediatric rule) may require further study of a product after approval.

IV. POLICY: DEFINITION OF AVAILABLE THERAPY

The regulations and policies described above, except the pediatric rule, do not explicitly define available therapy. CDER and CBER have determined that in regulations and policy statements, where the terms are not otherwise defined, *available therapy* (and the terms *existing treatments* and *existing therapy*) should be interpreted in almost all cases as therapy that is reflected in the approved labeling of regulated products.[2] In unusual

[2] Approved labeling refers to claims approved conventionally or under FDA's accelerated approval procedures.

cases, a treatment that is not FDA-regulated (e.g., surgery) or that is not labeled for use but is supported by compelling literature evidence (see the FDA guidance for industry on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)) can be considered available therapy.

Most of the Agency programs that use the term available therapy are intended to encourage the development and expedite the review of innovative drug products. By defining available therapy to focus upon approved products with labeling for use in the disease or condition at issue, FDA both emphasizes the importance of the approval process for establishing that a drug is safe and effective for a particular use, and provides the greatest opportunity for development and approval of appropriately labeled drugs. Products that are used off-label for the indication at issue and products that have not had formal FDA review are usually not considered available therapy for purposes of FDA regulations and policies. The definition of available therapy in this guidance provides a limited exception to this policy for particularly well documented therapies.

Note that the definition of available therapy in this guidance (which allows in unusual circumstances available therapy to include a treatment that is not FDA-regulated or that is not labeled for use) does not apply to the pediatric rule. Under the pediatric rule, a product provides meaningful therapeutic benefit over existing therapies if it would represent a significant improvement as compared to "marketed products adequately labeled for that use in the relevant pediatric population" (21 CFR 314.55(c)(5) and 601.27(c)(5)). As clearly described in the regulations, a key factor in assessing existing treatments to determine whether to require pediatric studies of a new product is whether available products are adequately labeled for pediatric use. This approach is based on the Agency's determination that the absence of pediatric labeling information poses a significant risk for children. This significant risk remains because, despite the long history of pediatric use of products, information about pediatric use generally is not included in the product labeling.

REFERENCES

FDA, *CDER Manual of Policies and Procedures (MAPP) 6020.3, Priority Review*, April 1996 (http://www.fda.gov/cder/mapp.htm)

FDA, *CBER Manual of Standard Operating Procedures and Policies 8405, Complete Review and Issuance of Action Letters*, May 1998 (http://www.fda.gove/cber/regsopp/8405.htm)

FDA guidance for industry on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) (http://www.fda.gov/cder/guidance/index.htm)

FDA guidance for industry on *Fast Track Drug Development Programs: Designation, Development, and Application Review* (September 1998) (http://www.fda.gov/cder/guidance/index.htm)